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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/520,502	01/03/2005	Christopher M Ward	021911.001110US	2720

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EXAMINER
NOBLE, MARCIA STEPHENS

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/520,502	WARD ET AL.	
	Examiner	Art Unit	
	Marcia S. Noble	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,8-10 and 14* is/are pending in the application.

4a) Of the above claim(s) *7,11-13 and 15-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-10 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 January 2005* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/29/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Claims

1. Applicant's election with traverse of Group I, claims 1-6, 8, and 14, with a species election of human for claim 5, in the reply filed on 5/15/06 is acknowledged. The traversal is on the ground(s) that the groups have the same inventive step and that Southhall et al does not anticipate the instant invention disclosed in claim 1 because cancer cells and stem cells are substantially and significantly different. Applicant argues:

"Stem cells can differentiate into multiple cell types, and in the case of pluripotent stem cells into essentially all cell types found in the adult organism. Cancer cells, while they appear undifferentiated, have no such potential. Furthermore, it has long been known that antigens which are found specifically on cancer cells are not found on embryonic stem cells and vice versa. Therefore, the identification of a marker antigen on a cancer cell as disclosed by Southall et al. does not include or suggest the appearance of the same marker antigen on a stem cell." (p. 3 par 4 of response)

This is not found persuasive because the breadth of claim 1 would encompass some cancer cells. There is evidence that some cancer cells would be considered stem cells because, as stated in the restriction, they are characteristically clonal and undifferentiated. Examiner disagrees with the argument that cancer cells do not have differentiation potential, this is clear not the case in terms of dermoid cancer cells develop into hair and bone tissue or embryonic carcinoma cells lines as well. Applicant argues that antigens which are found on cancer cells are not found on embryonic cells

and vice versa. This is also inaccurate. Cancer cells and embryonic cells share many cells surface markers in common, such as integrins. Furthermore, this argument is in conflict with the instant invention where 5T4 antigen is found on cancer cells as well as embryonic cells as discussed in the instant invention. The reasons disclosed above the restriction requirement stands.

However, after further consideration, it was determined that a search of group III in addition to group I would not serve as a serious additional search burden, nor would examination of all the species of claim 5. Therefore, Group III, claims 9 and 10, will be rejoined with Group I, claims 1-6, 8, and 14, and the species election for claim 5 is withdrawn.

The requirement is still deemed proper and is therefore made FINAL.

Claims 7, 11-13, and 15-19 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 5/15/06.

Claims 1-6, 8-10, and 14 are under consideration.

Priority

2. Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant claims foreign

priority to UK 0215287(7/02/2002). Applicant has complied with conditions for receiving the benefit of an earlier filing date.

Information Disclosure Statement

3. The information disclosure statement (IDS) submitted filed on 4/29/05 & 4/1/05. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered. References are listed on pages 67-71 of the specification and should be removed.

Specification

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Hyperlinks were pages 14, 21, and 22 of the specification and should be removed.

Drawings

5. The drawings are objected to as failing to comply with 37 CFR 1.84(p)(5) because they include the following reference character(s) not mentioned in the description: Figure 22 a and b. Corrected drawing sheets in compliance with 37 CFR 1.121(d), or amendment to the specification to add the reference character(s) in the description in compliance with 37 CFR 1.121(b) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Figures 16, 17b&c, 22a&b, 24, 24-27 are incomprehensible and therefore submission of drawing with better images is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-6, 8-10, and 14 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising detecting the presences of 5T4 antigen in mouse embryonic stem (mES) cells or human embryonic carcinoma (hEC) cells comprising incubating a sample of mES cells or hEC cells with a labeled anti5T4 antibody such that specific binding of the antibody to 5T4 cell surface antigen on mouse ES cells or hEC cells occurs and detecting and sorting of mES cells or hEC cells on the basis of presence or absence of 5T4 antibody following the incubation, does not reasonably provide enablement for a method of detecting the differentiation status of any stem cell comprising detecting the presence or absence of 5T4 antibody on the surface stem cells wherein the presence of 5T4 agent represents stem cells in a more differentiated state and the absence of 5T4 antigen identifies undifferentiated or pluripotent stem cells. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

While determining whether a specification is enabling, one considers whether the claimed invention provides sufficient guidance to make or use the claimed invention, if not, whether an artisan would require undue experimentation to make and use the

claimed invention and whether working examples have been provided. When determining whether a specification meets the enablement requirements, some of the factors that need to be analyzed are: the breadth of the claims, the nature of the invention, the state of the prior art, the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples, and whether the quantity of any necessary experimentation to make or use the invention based on the content of the disclosure is "undue".

Furthermore, USPTO does not have laboratory facilities to test if an invention will function as claimed when working examples are not disclosed in the specification, therefore, enablement issues are raised and discussed based on the state of knowledge pertinent to an art at the time of invention, therefore skepticism raised in the enablement rejections are those raised in the art by artisans of expertise.

The critical component and novelty of the instant invention is the finding that 5T4 antigen is found on the surface of some hEC and mES cells. The 5T4 antigen is disclosed as identifying two populations of cells in a sample of ES cells or hEC cells. Those cells that have 5T4 antigen present on their cell surface identified by a 5T4 antibody or express the gene for 5T4 antigen, and those cells that do not. The specification discloses that mES cells, OKO160 and MESC, show no or low levels, as claimed, of 5T4 antigen, but once LIF has been withdrawn the number of 5T4 antigen expressing cells increase over time (p. 56, lines 25-30). The specification discloses that the expression patterns of 5T4 antigen is consistent with other reportered stem cell markers, such as SSEA, and their expression patterns as during the process of

differentiation. The specification suggest that 5T4 antigen may even serve as a better marker of differentiation status because cells that were 5T4- but SEEA+ were fund to have 52% pluripotency as compared the 7% pluripotency for cells positive for both markers. Pluripotency was measured by efficiency of cells to incorporate into chimeric mice (p. 60, lines 14-29). The specification also discloses that hEC with some limited potency adapted to growth on gelatin were strongly positive for 5T4 antigen sorted by FACS. In contract, hEC cell grown on mouse fibroblast were negative for 5T4 antigen (p. 64, lines 22-29).

Although the specification indicates that both mES cells and hEC cells are negative for 5T4 antigen at a time/culture condition that corresponds to less differentiation and potential for pluripotency and positive for 5T4 antigen in culture condition that is conducive to differentiation, these results do not demonstrate that 5T4 antigen is a definitive marker of differentiation or an indicator of pluripotency. The specification did not demonstrate that these cells have the ability to become multiple tissue types. The specification does demonstrate that 52% a isolated population of 5T4 antigen negative mES cells were capable of incorporating into chimeras. However, incorporation of mES cell is not a measure of differentiation. The formation of a chimera indicates that stem cells were present and were in a state wherein they could develop in a tissue and incorporate into formation of an animal. Although it suggests that stem cells that to some degree are less differentiated were present, it does not determine the level of differentiation nor does it demonstrate its contribution to the animal. It is possible that some of the cells incorporate into the animal but do not divide therefore

not contributing to the development of the animal. Overall very little is known about what happen to a ES cell in chimeric formation and at what point an ES cell is not capable of incorporating into an ES cell, therefore, the formation of a chimeric provides little information about the state of differentiation of a cell. Furthermore, 48% of the 5T4 antigen negative mES cell did not incorporate into chimeras. Although there mostly likely are multiple reasons for why an mES cell did not incorporate into a chimera, one is that a proportion of those cells may have been differentiated. These results do demonstrate that even a population determined 5T4 antigen negative mES cells is still a heterogeneous population of mES cells that still have different differentiation and pluripotency potentials. Terefore, an artisan would not know how to use or make the instant invention to determine differentiation status or pluripotency potential from the instant specification.

As acknowledge by the instant specification, at the time of filing and to date there are no marker that can accurately assess differentiation status and pluripotency potential of ES cells (p. 2 lines 28-29). Given that the art does not provide good markers of differentiation status and pluripotency potential of ES cells, the specification would need to demonstrate that the 5T4 antigen is truly a measure of differentiation status and pluripotency potential of ES cells. Since the specification does not adequately demonstrate 5T4 antigen as a definitive marker for differentiation status and pluripotency potential, an artisan would not know how to use it as such. Furthermore, an artisan would have to do further experimentation to determining if cells identified and

isolated based of its lack of 5T4 antigen truly can develop into any tissue/cell type. This level of experimentation is considered undue.

The instant invention claims murine, human, primate, porcine, feline, bovine, ovine or canine stem cells. However, the present state of the art is that ES cell have only been developed in mouse and humans. Since the art does not provide established ES cells for any other species than human and mouse, an artisan would look to the specification for guidance on obtaining, testing, and using ES cells of other species. The specification only provides guidance for mES and hEC cells, therefore it only enables mES and hEC cells. Similarly, the instant invention claims any stems cells, however, the specification nor the art provide any evidence that 5T4 antigen will be present on any other stem cells or that it will be an indication of differentiation status or pluripotency potential. Therefore, an artisan would not know how to use 5T4 antigen in the instant method with other species of ES cells or any other type of stem cells. An artisan would have to determine if these other types of stems cells express 5T4 antigen and if its expression pattern is evidence of differentiation status or pluripotency. Again, this level of experimentation is considered undue.

Therefore, given the insufficient guidance in the art and specification, the instant invention is only enabled for a method of identifying 5T4 antigen on mES and hEC cell and are not enabled for a method of determining differentiation status in any stem cells.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 2 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "low level" in claim 2 is a relative term which renders the claim indefinite. The term "low level" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

8. Claims 1, 3, 5, 6, 8, and 14 are rejected under 35 U.S.C. 102(b) as being anticipated by Southall et al (Br J Cancer 61:89-95, 1990).

The instant invention is drawn to an antibody detection method comprising detecting the expression of 5T4 antigen in stem cells.

Southall et al discloses a method using an antibody again 5T4 to discern the normal tissues from various cancer tissues, such as carcinomas of the bladder, breast, cervix, endometrium, lung, oesophagus, lung, ovary, pancreas, stomach, and testicular non-seminomatous germ cell tumors using an antibody against 5T4 antigen. Due to the breadth of the claims to any stem cell and because most carcinomas are

characteristically clonal and undifferentiated, they can be considered stem cells (see abstract, figures 1 and 2 and Tables on pages 91-93).

9. Claims 9 and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Boyle et al (Hum Genet 84:455-458, 1990).

The instant invention is drawn to method comprising binding cells with anti-5T4 antibody, separating cells with bound antibody from cells with no bound antibody and isolating viable cells.

Boyle et al discloses trophoblast and cancer cells that were sorted by FACS analysis using an antibody against 5T4 antigen. Because little to no patentable weigh need be given to the preamble disclosing a purpose for the method, as is the instant case, Boyle et al anticipated the instant method.

Conclusions and Relevant Art

10. Overall, given the breadth of the claims and the lack of guidance provided by the specification, the instant invention was not enabled for its intended use. A review of the art does indicate that the finding of 5T4 antigen on mES and hEC cells is novel and has great potential for a stem cell marker. However, the specification did not provide enough support that the instant invention was a marker of differentiation status as claimed. The inventors have published the instant invention as described in the examples in post filing art (Ward et al J Cell Sci 116(22);4533-4542 and Ward et al Exp

Cell Res. 2006 Apr 14; [Epub ahead of print]). However, the post-filing art does not overcome any of the enablement issues previously discussed.

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marcia S. Noble whose telephone number is (571) 272-5545. The examiner can normally be reached on M-F 9 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Marcia S. Noble